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Via courier:
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Date 24.10.2003
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Draft Guidance for Industry:
PAT - A Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance

Docket No. 2003D-0380

Dear Sir/Madam

Merck KGaA, Germany is a manufacturer of active ingredients for drug products since 1827. Today Merck is operating in the business sectors Pharmaceuticals, Chemicals and Laboratory Distribution organized in different divisions. As a pharmaceutical company, Merck KGaA develops and markets prescription drugs to satisfy unmet medical needs in large patient populations. We supply customers throughout the world including the USA.

Therefore we are affected by the "Draft Guidance for Industry:
PAT - A Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance".

We appreciate very much the opportunity to provide comments on this draft guidance for industry. Please find the comment attached.

Sincerely,

Merck KGaA, Germany

i.V. Dr. Oelrich

i.A. Dr. Büttgenbach

2003D-0380

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Merck KGaA, Germany Comments on Guidance for Industry: PAT - A Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance

Docket No. 2003D-0380

General Comments

We appreciate the FDA initiative of risk-based approach to enhance the process of implementation of new technologies in the pharmaceutical production.

We understand that the PAT covers voluntary development and implementation of innovative pharmaceutical manufacturing and quality assurance for drug substances and drug products. We would like to emphasize that PAT-technologies voluntary developed for specific production processes will not be expected by the authority to be implemented in other production processes by expecting compliance to cGMP. Especially established production processes of approved applications should be protected against this prospect.

Development and implementation of PAT-technologies should be focused critical on production steps that are difficult to control. Processes that are known as robust by operating over several years of production should generally not be subjected to this approach.

The draft guideline proposes a regulatory approach to assist the industry by the PAT-process. This gives FDA a detailed knowledge of the production processes. In this case we expect a certain enhanced regulatory approval of the amendment. However PAT requires the established regulatory procedures for the amendments of changes in production processes. If a pharmaceutical manufacturer voluntarily implements PAT he

should reap the benefit of decreased regulatory requirements for filling of the amendment. This should be clearly stated by the guidance.

Specific comments

p .6, line 102-107
Here the guideline says that regulatory policies must rise to the challenge of new discoveries and ways of doing business. It remains unclear how this should be understood in detail. For instance does it mean in case of archiving of experimental electronic process data that the industry has to follow the requirements of CFR 21 Part 11?

p. 7, line 138-149
We understand that the suggested characterization of the desired future state of pharmaceutical manufacturing is not ment to be applicable in total to every specific manufacturing process. In fact many manufacturing processes will fulfill this requirements only partially.

p. 7, line 140-141 and p. 18 line 622-624
The guideline uses the term "mechanistic understanding" of formulation and process. In addition manufactures are encouraged to develop "mechanistic-based regulatory specifications". In these cases it would be helpful to get a clear description of the understanding about "mechanistic" in detail.

p. 7, line 142
The term continuous real time quality assurance needs to be explained in detail. E.g. we do not expect that it is applicable to microbiological quality parameters. The scope of methods should be defined.

p. 8, line 189-191
During pre-formulation programs the data should regarded as research data and not relevant concerning to GMP.

p. 12, line 350-351
The parameter "absorption" is known as a pharmaceutical term and in the context with PAT not applicable. It should be deleted.

p. 14, line 457-458
It is not described which part of the large volumes of data from real time measurement tools are recommended to archive. This should be explained more in detail. Criteria for the selection of data should be provided.

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Executive Board and General Partners:
Bernhard Scheuble (Chairman),

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p. 15, lines 481-486
For the validation of PAT software the guideline suggests a risk-based approach. This is appreciated. On the other hand the cited guidance tighten this advantage considerably. Their application should not be required.

p. 16, lines 541-543
The guideline announces "less restrictive regulatory approaches to manage change" for processes that are well understood. This is an appreciated suggestion. On the other hand industry needs clear descriptions of the regulatory advantages rised by PAT for a concrete decision making.

p. 18, lines 626-633
PAT suggests the evaluation of experimental data in approved manufacturing processes by installation of experimental tools in the production. Concerning possible inspections of the approved production process it is considered to be essential to give certain criteria to distinguish between process controls in research status and routine process controls.

p. 19, lines 661-669
We expect that PAT will have an influence on the classification of change amendments. Therefore concrete classification criteria for PAT are required.

p. 19, lines 696-701
In contradiction to p.16 lines 541-543 the guideline requires to follow all relevant FDA guidance documents concerning change reports. This point has to be clarified more detailed.